An unexpected Mitsunobu reaction. A direct route to the 2,5-diazabicyclo[2.2.1]heptan-3-one skeleton as a γ-lactam mimic of β-lactam antibiotics

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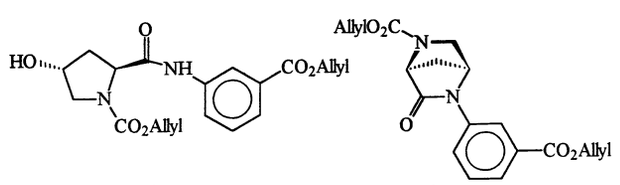
Treatment of anilides of *N*-protected (2*S*,4*R*)-4-hydroxyproline, *e.g.* 1, with thioacetic acid under Mitsunobu conditions gives, unexpectedly, 2,5-diazabicyclo[2.2.1]heptan-3-ones, *e.g.* 2, the products of intramolecular cyclisation. However, the less acidic *N*-benzylamides of these proline derivatives, *e.g.* 7, are not sufficiently acidic and the hydrazido anion generated in the Mitsunobu reaction displaces the activated hydroxy group in an intermolecular reaction to give 8. The bicyclic γ-lactams are potential analogues of the β-lactam antibiotics and suitable derivatives 9, 10, 11 and 12 are found to be competitive inhibitors of class A and C β-lactamases, with K_i as low as 70 μM.

The antibacterial activity of β-lactam antibiotics was, for many years, thought to be intimately related to the four-membered ring and the non-planarity of the lactam nitrogen.[1] However, the chemical reactivity of penicillins and cephalosporins is not unusual and the rate of the ring opening reactions of these derivatives does not indicate any significant release of strain energy or loss of amide resonance.[2] The basic requirement for biological activity appears to be an effective acylating agent of the bacterial transpeptidase enzyme coupled with sufficient molecular recognition.[2] Reactivity can be reflected in the rates of alkaline hydrolysis, which, for penicillins and cephalosporins, typically have second order rate constants k_{OH} of 0.1 to 10 $dm^3\ mol^{-1}\ s^{-1}$.[2] The molecular shape of an effective β-lactam antibiotic requires an acidic group with a separation of about 3.0–3.6 Å between the lactam carbonyl carbon and the centre of the acidic group.[3] Considering these simple requirements there have been several attempts to design isosteres of β-lactams which are not four-membered rings. Most of these mimics have been γ-lactams,[4,5] particularly pyrazolidinones,[6] imidazolidinones,[7] cycloserines[8] and hydantoins.[9] We report here the synthesis of a novel bicyclic γ-lactam as a potential isostere for the β-lactam antibiotics using the Mitsunobu reaction.

The normal Mitsunobu reaction involves the S_N2 displacement of an activated hydroxy group by an acidic function like a carboxylic acid or imide.[10,11] In a few special circumstances, less acidic nucleophiles can perform the displacement reaction intramolecularly.[10] This paper provides an example of an intramolecular Mitsunobu reaction in which an amide acts as the nucleophile. However, if the acidity of the amide is reduced, an intermolecular reaction takes precedence over the intramolecular one.



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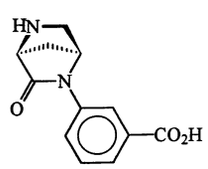

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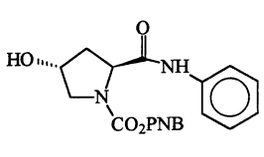

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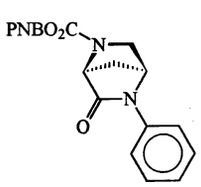

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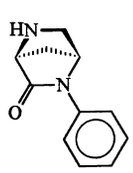

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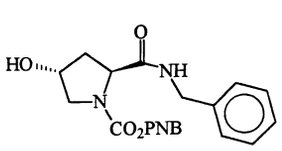

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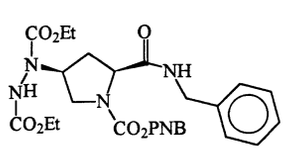

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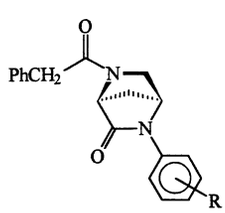
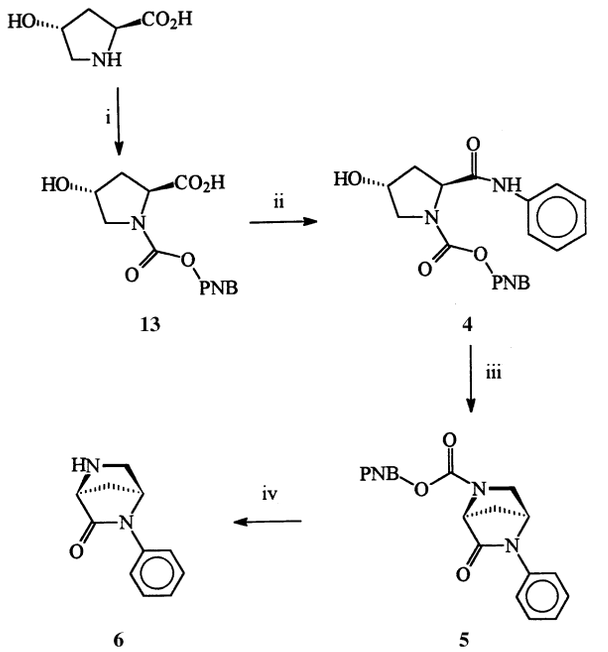


	R
9	*m*-CO_2H
10	*o*-CO_2H
11	*p*-NO_2
12	*o*-NO_2

Results and discussion

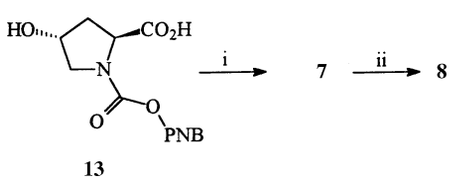
We were exploring ways of converting the *N*-protected (2*S*,4*R*)-4-hydroxyproline amide **1** to the corresponding (4*S*)-thiol. One way of achieving this conversion is by mesylation of the hydroxy group and displacement of the methanesulfonate with the sodium salt of thioacetic acid;[12] the thioacetate can then be hydrolysed to the corresponding thiol under mild conditions. When this conversion was tried on **1** using thioacetic acid and Mitsunobu conditions, the bicyclic product **2** was obtained in about 60% yield and the same product was isolated when the thioacetic acid was left out of the reaction mixture.

The allyl protecting groups were easily removed using palladium chemistry giving the amino acid **3**. The simpler and slightly less acidic anilide **4** formed a similar bicyclic product **5** in about the same yield under the reaction conditions (Scheme 1). The 4-nitrobenzyl (PNB) protecting group was removed



Scheme 1 *Reagents and conditions:* i, *p*-nitrobenzyl chloroformate, NaOH, 0 °C; ii, aniline, EEDQ, toluene, room temp.; iii, TPP, DEAD, THF, −10 °C; iv, 10% Pd/C, H_2, THF, room temp.

from **5** by hydrogenation to give **6**. Interestingly, the benzyl amide **7** did not cyclise in this way and the intermolecular product **8** was isolated, arising from S_N2 displacement of the activated hydroxy group by the hydrazino anion generated under Mitsunobu conditions (Scheme 2). Clearly the limits of amide



Scheme 2 *Reagents and conditions:* i, isobutyl chloroformate, Et_3N, −10 °C, benzylamine; ii, TPP, DEAD, THF, −10 °C

activity had been reached for the intramolecular Mitsunobu cyclisation.

Related bicyclo systems have been synthesised from (2*S*,4*R*)-4-hydroxyproline by the following longer sequence; *N*-protection of the amine, esterification of the acid, mesylation of the hydroxy group, S_N2 displacement of the methanesulfonate by azide, reduction of the azide to an amine, hydrolysis of the ester to the acid and cyclisation to the amide with dicyclohexylcarbodiimide or similar reagent.[13]

Interestingly, these bicyclic amides are strained to some extent (IR ~1720–1730 cm^{-1}) and have the same absolute stereochemistry as the classical β-lactams, the penicillins and cephalosporins. The analogues **9**, **10**, **11** and **12** were therefore synthesised carrying the penicillin G side-chain **14**. Models indicated that the amide and the carboxy group in both **9** and **10** were reasonable overlays on some of the more rigid β-lactam structures (Fig. 1). The preferred position for this carboxy group is a matter of some debate.[3] There is considerable variation in its spatial orientation among the known β-lactam structures. The nitro compounds **11** and **12** were synthesised for two reasons. Firstly, the nitro group in both compounds will

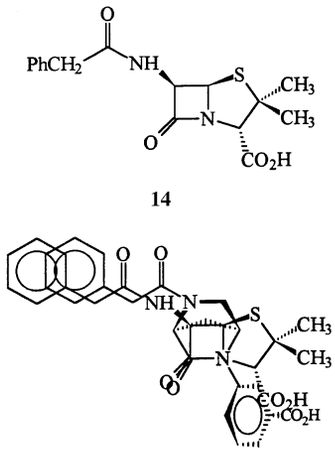


Fig. 1 Overlay of Penicillin G **14** on bicyclic analogue **9**

activate the lactam carbonyl to attack, and substitution, by nucleophiles and proteolytic enzymes; secondly, the nitro group has been used previously as an isosteric mimic of the carboxylate anion.[14] The first stage in the synthesis of **9**–**12** was *N*-protection of the (2*S*,4*R*)-4-hydroxyproline as a carbamate to give **15** (Scheme 3). 1-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) was used to make the proline amides since this reagent allows formation of the mixed carbonic anhydride in the presence of the amino component,[15] which is necessary to avoid intermolecular esterification by the hydroxy moiety.

The slightly lower yielding reactions, *i.e.* 54 and 47%, respectively, giving **17** and **18** may be attributed to the reduced nucleophilicity of the nitro anilines.

The Mitsunobu conditions provided a convenient route to the bicyclic γ-lactam compounds which after deallylation, using palladium chemistry, yielded the corresponding amino acids and amines. Acylation of the amino acid **3** and its isomer with the carboxy group in the *o*-position provided the synthetic route to **9** and **10**; the corresponding nitro amines were the precursors of **11** and **12**. The synthesis of the other starting materials can be found in the experimental section.

Inhibition studies

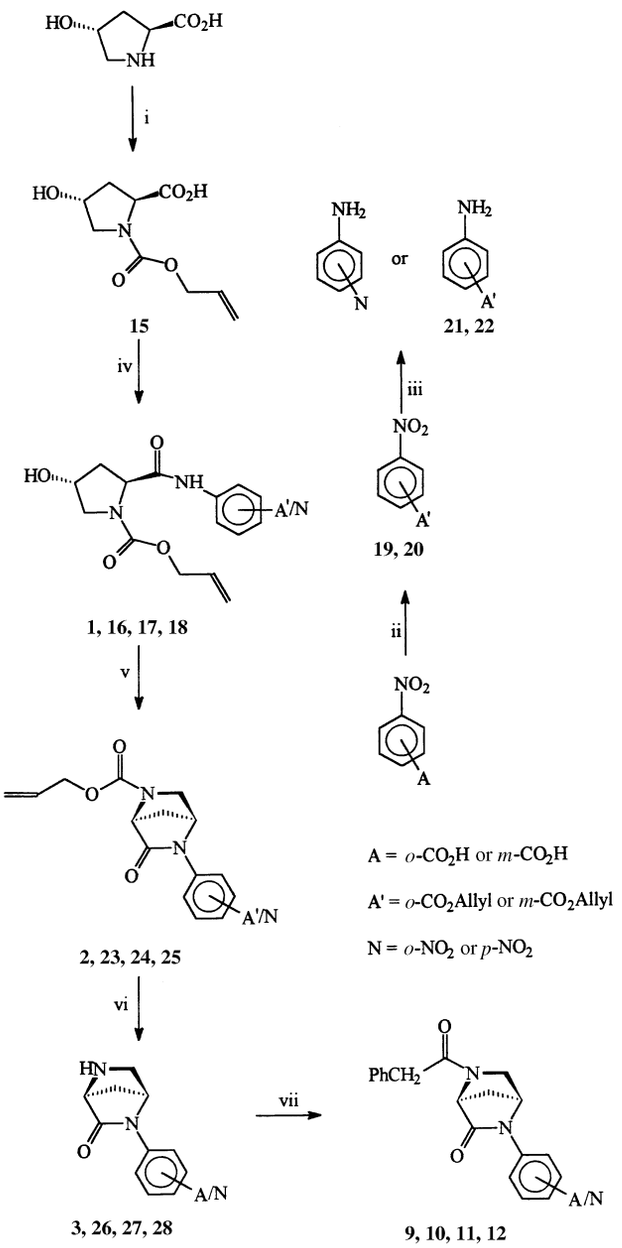
The bicyclic γ-lactams were tested for inhibition of the β-lactamase enzymes from *Bacillus cereus* 569/H class A and class B and the class C enzyme from *Enterobacter cloacae* P99. The class A and C β-lactamases are serine enzymes whereas the class B is a zinc dependent enzyme.[16] The conditions for the experiments were ionic strength 1.0 M (KCl), 30 °C, pH 7.4 buffer solution using cephaloridine as substrate.

The γ-lactams are selective competitive inhibitors of the β-lactamase enzymes and the associated inhibition constants K_i are given in Table 1. In general, only weak or no inhibition was found with the metallo-enzyme. However, inhibition is substantial for the serine enzymes. The γ-lactam **11** is a good inhibitor with a K_i of 90 μM for the class A β-lactamase and 71 μM for the class C enzyme. These observations are very encouraging and are the subject of further investigation.

The γ-lactams were also screened for antibacterial activity against a wide range of micro-organisms but they showed no significant activity up to a concentration of 128 μg cm^{-3}.

Experimental

Mps were determined on a Gallenkamp melting point apparatus and are uncorrected. 270 MHz ^1H and 67 MHz ^{13}C NMR Spectra were determined on a Bruker AC-270 spectrometer with tetramethylsilane as internal standard. All *J* values are given in Hz. IR Spectra were recorded on a Perkin-Elmer 1600 series FTIR and FAB MS were performed by Swansea Mass Spectrometry Service and Zeneca Pharmaceuticals. All elemental



Scheme 3 *Reagents and conditions:* i, allyl chloroformate, NaOH, 0 °C; ii, K_2CO_3, allyl bromide, DMF, room temp.; iii, $Sn^{II}Cl_2$, MeOH, room temp.; iv, EEDQ, toluene, **21** or **22**, room temp.; v, TPP, DEAD, THF, −10 °C; vi, $[P(Ph)_3]_4Pd^0$, Meldrum's acid, CH_2Cl_2, room temp.; vii, phenylacetyl chloride, Et_3N, DMF, 0 °C

analyses were performed by MEDAC Ltd, Brunel University. Fluka silica gel 60 was used for all chromatographic separations and thin layer chromatographic techniques used Merck silica gel 60 F_{254} TLC plates. Ether refers to diethyl ether. Tetrahydrofuran was dried by distilling over lithium aluminium hydride under dry nitrogen. Dichloromethane was dried by passing it through a column of Grade I activated alumina into the reaction flask under argon.

Method A: allyloxycarbonyl protected (2*S*,4*R*)-4-hydroxyproline 15

(2*S*,4*R*)-Hydroxyproline (30.50 g, 0.233 mol) was dissolved in 2 M aqueous sodium hydroxide (230 cm^3) and cooled to 0 °C with stirring. To this was added simultaneously allyl chloroformate (28.04 g, 0.233 mol) and 4 M aqueous sodium hydroxide (60 cm^3) at such a rate that both reagents had been added at the end of 1 h. The reaction was left for a further 3 h before the addition of conc. hydrochloric acid to take the reaction mixture to pH 2. This was then extracted using EtOAc, the combined organics dried using anhydrous $MgSO_4$, filtered and evaporated to dryness to yield **15** (45.54 g, 91%) as a colourless oil which later crystallised, mp 67–69 °C (Found: C, 49.9; H, 6.1; N, 6.4. $C_9H_{13}NO_5$ requires C, 50.2; H, 6.1; N, 6.5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3410, 1725, 1686, 1439, 1415, 1344, 1216 and 757; $\delta_H([^2H]_6$ DMSO) 1.85–2.25 (2 H, m, proline CH_2), 3.37 (1 H, br s, OH), 3.40 (2 H, m, NCH_2), 4.22 (2 H, m, single Hs at 2 and 4 positions of proline ring), 4.50 (2 H, m, OCH_2), 5.12–5.33 (2 H, m, CH=CH_2), 5.88 (1 H, m, C*H*=CH_2), 12.60 (1 H, br s, CO_2H); *m/z* (CI+) 216 $(M + H)^+$, 198, 170, 154, 132, 126, 108 and 86.

(2*S*,4*R*)-1-(*p*-Nitrobenzyloxycarbonyl)-4-hydroxyproline 13. Method A was used in the synthesis of **13** using (2*S*,4*R*)-4-hydroxyproline (37.50 g, 0.286 mol), *p*-nitrobenzyl (PNB) chloroformate (66.00 g, 0.286 mol) and 4 M aqueous sodium hydroxide (150 cm^3) to give **13** (80.0 g, 90%) as a white solid, mp 181.6–182.6 °C (Found: C, 50.0; H, 4.6; N, 9.0. $C_{13}H_{14}N_2O_7$ requires C, 50.3; H, 4.6; N, 9.0%); $\delta_H([^2H]_6$ DMSO) 1.85–2.25 (2 H, m, proline CH_2), 3.30 (1 H, br s, OH), 3.40 (2 H, m, NCH_2), 4.28 (2 H, m, single Hs at 2 and 4 positions of proline ring), 5.20 (2 H, m, OCH_2), 7.60 (2 H, m, aryl), 8.20 (2 H, m, aryl), 12.65 (1 H, br s, CO_2H); *m/z* (CI+) 311 $(M + H)^+$, 333 $(M + Na)^+$.

Method B: allyl 3-nitrobenzoate 19

3-Nitrobenzoic acid (50.0 g, 0.30 mol) was dissolved in DMF (700 cm^3) at room temperature with stirring. To this was added potassium carbonate (82.70 g, 0.60 mol) slowly. Effervescence and a small exotherm were observed followed by the formation of a thick white suspension. Allyl bromide (54.44 g, 0.45 mol) was added and the reaction mixture was stirred for 18 h over which time disappearance of the thick white suspension occurred and a white particulate solid formed. The reaction mixture was filtered through a pad of Celite washing well with CH_2Cl_2 and then EtOAc. Evaporation to dryness gave a viscous yellow oil which was taken up into ether and washed with saturated aqueous sodium hydrogen carbonate. The aqueous layer was further extracted using ether and the organics combined and washed with water, 2 M HCl, water and saturated brine. The organic layer was dried using anhydrous sodium sulfate, filtered and evaporated to yield **19** (62.08 g, 100%) as a yellow oil (Found: C, 58.1; H, 4.4; N, 6.7. $C_{10}H_9NO_4$ requires C, 58.0; H, 4.35; N, 6.8%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3089, 3057, 2950, 1727, 1617, 1535, 1351, 1265, 1135 and 738; $\delta_H(CDCl_3)$ 4.89 (2 H, dd, *J* 5.8 and 1.6, OCH_2), 5.38 (2 H, m, CH=CH_2), 6.05 (1 H, m, C*H*=CH_2), 7.68 (1 H, t, *J* 8.2, aryl), 8.41 (2 H, dd, *J* 8.2 and 1.9, aryl) and 8.88 (1 H, dd, *J* 2.0 and 1.9, aryl); *m/z* (GC–MS) 208 $(M + H)^+$, 177, 157, 150, 134, 121, 104, 92, 81 and 76.

Allyl 2-nitrobenzoate 20. Method B was used in the preparation of **20** using 2-nitrobenzoic acid (20.00 g, 0.12 mol), potassium carbonate (33.17 g, 0.24 mol), allyl bromide (21.78 g, 0.18 mol) and DMF (300 cm^3) yielding **20** (23.85 g, 96%) as a brown oil (Found: C, 58.2; H, 4.5; N, 6.7. $C_{10}H_9NO_4$ requires C, 58.0;

Table 1 Inhibition constants K_i for the inhibition of β-lactamase by the bicyclic γ-lactams

Inhibitor	β-Lactamase	K_i/μM
9	Class A	681
	Class B	$\geq 10^4$
	Class C	417
10	Class A	182
	Class B	$>10^4$
	Class C	2410
11	Class A	90
	Class B	605
	Class C	71.4
12	Class A	395
	Class B	586
	Class C	517

H, 4.35; N, 6.8%); ν_{max}(thin film)/cm^{-1} 3451, 3088, 2948, 2880, 1734, 1539, 1360, 1294, 1128, 1073, 941, 790 and 736; δ_H($CDCl_3$) 4.82 (2 H, dd *J* 4.7 and 1.3, OCH_2), 5.35 (2 H, m, CH=CH_2), 5.98 (1 H, m, C*H*=CH_2), 7.64–7.77 (3 H, m, aryl) and 7.91 (1 H, dd, *J* 7.3 and 1.4, aryl); *m/z* (GC–MS) 208 (M + H)$^+$ 191, 177, 150, 134, 121, 104, 92, 81, 65, 51 and 39.

Method C: allyl 3-aminobenzoate 21

Allyl 3-nitrobenzoate **19** (62.0 g, 0.3 mol) was dissolved in methanol (480 cm^3) with electric stirring at room temperature and the apparatus was fitted with a reflux condenser. Tin(II) chloride (338.45 g, 1.5 mol) was added slowly over 5 min and the temperature rose very quickly to reflux. When the reflux eventually ceased (10 min) the reaction cooled and was stirred for a total of 1.5 h. The mixture was evaporated to dryness to give an orange oil. The oil was redissolved in EtOAc (800 cm^3) and conc. ammonia added with external ice bath cooling and electric stirring. A thick white precipitate formed and addition of ammonia was stopped when the pH of the solution reached pH 13. The suspension was filtered through a pad of Celite washing well with EtOAc and the organics concentrated to a usable volume. This was washed with 2 M aqueous ammonia, water and then brine, dried using $MgSO_4$, filtered and evaporated to yield **21** (51.93 g, 98%) as an orange oil (Found: C, 67.6; H, 6.4; N, 7.8. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); ν_{max}(CH_2Cl_2)/cm^{-1} 3468, 3377, 3054, 1713, 1624, 1461, 1292, 1101 and 754; δ_H($CDCl_3$) 3.81 (2 H, br s, NH_2), 4.80 (2 H, m, OCH_2), 5.34 (2 H, m, CH=CH_2), 6.01 (1 H, m, C*H*=CH_2), 6.85 (1 H, m, aryl), 7.22 (1 H, t, *J* 7.8, aryl), 7.36 (1 H, m, aryl) and 7.45 (1 H, m, aryl); *m/z* (GC–MS) 177 (M)$^+$, 160, 150, 132, 120, 103, 75, 93, 65, 52 and 39.

Allyl 2-aminobenzoate 22. Method C was used in the preparation of **22** using allyl 2-nitrobenzoate **20** (23.50 g, 0.114 mol), tin(II) chloride (128.61 g, 0.570 mol) and methanol (200 cm^3) yielding **22** (19.57 g, 97%) as an orange oil (Found: C, 67.8; H, 6.25; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); ν_{max}(CH_2Cl_2)/cm^{-1} 3494, 3378, 3054, 2986, 1690, 1617, 1589, 1265, 1245, 1106 and 738; δ_H($CDCl_3$) 4.77 (2 H, m, OCH_2), 5.35 (2 H, m, CH=CH_2), 5.72 (2 H, br s, NH_2), 6.02 (1 H, m, C*H*=CH_2), 6.64 (1 H, td, *J* 7.6 and 1.8, aryl), 6.66 (1 H, d, *J* 7.6, aryl), 7.26 (1 H, m, aryl) and 7.90 (1 H, dd, *J* 7.6 and 1.8, aryl); *m/z* (GC–MS) 177 (M)$^+$, 130, 120, 92, 65, 52 and 39.

Method D: (2*S*,4*R*)-1,3′-bis(allyloxycarbonyl)-4-hydroxyprolinanilide 1

1-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (22.40 g, 91.0 mmol) was added to a mixture of allyloxycarbonyl protected (2*S*,4*R*)-4-hydroxyproline **15** (15.00 g, 70.0 mmol) and allyl 3-aminobenzoate **21** (13.57 g, 77.0 mmol) in toluene (750 cm^3) at room temperature with stirring. The mixture was stirred using an electric stirrer for 18 h before being evaporated to dryness, taken up into EtOAc and washed with 2 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate, brine, dried using sodium sulfate, filtered and evaporated to give the crude product (29.40 g). Purification was achieved on a silica gel column using a gradient elution 100% CH_2Cl_2 to 100% EtOAc yielding **1** (20.84 g, 80%) as white crystals, mp 91–92 °C (Found: C, 61.0; H, 5.9; N, 7.5. $C_{19}H_{22}N_2O_6$ requires C, 60.95; H, 5.9; N, 7.5%); ν_{max}(CH_2Cl_2)/cm^{-1} 3323, 3055, 2986, 2949, 1708, 1681, 1649, 1597, 1556, 1440, 1414, 1268, 1187, 1117 and 738; δ_H([^{2}H]$_6$DMSO, 70 °C) 1.99–2.22 (2 H, m, proline, CH_2), 3.47–3.61 (2 H, m, NCH_2), 4.37 (1 H, br d, *J* 2.9, OH), 4.45–4.53 (3 H, m, C*H*OH and NCO_2CH_2), 4.79–4.86 (3 H, m, NC*H* and aryl CO_2CH_2), 5.10–5.45 (4 H, m, 2 × CH=CH_2), 5.90 (1 H, br m, carbamate C*H*=CH_2), 6.02 (1 H, m, aryl C*H*=CH_2), 7.43 (1 H, t, *J* 7.9, aryl), 7.67 (1 H, m, aryl), 7.87 (1 H, m, aryl), 8.26 (1 H, m, aryl) and 9.99 (1 H, s, NH); δ_C([^{2}H]$_6$DMSO, 70 °C) 40.24 (1 C, proline CH_2), 55.26 (1 C, NCH_2), 59.66 (1 C, HOCH), 65.01 (2 C, 2 × OCH_2), 68.43 (1 C, NCH), 116.56 (1 C, carbamate CH=*C*H_2), 117.85 (1 C, aryl CH=*C*H_2), 120.34 (1 C, aryl), 124.01 (1 C, carbamate *C*H=CH_2), 124.16 (1 C, aryl *C*H=CH_2), 128.91 (1 C, aryl), 130.35 (1 C, quat., aryl), 132.61 (1 C, aryl), 133.30 (1 C, aryl), 139.33 (1 C, quat., aryl), 154.19 (1 C, NC=O), 165.29 [1 C, NC(O)O] and 171.08 [1 C, C*C*(O)O]; *m/z* (FAB+) 375 (M + H)$^+$, 357, 317, 316, 198, 170, 126 and 108.

(2*S*,4*R*)-1,2′-Bis(allyloxycarbonyl)-4-hydroxyprolinanilide 16. Method D was used in the preparation of **16** using EEDQ (11.20 g, 45.0 mmol), allyloxycarbonyl protected (2*S*,4*R*)-4-hydroxyproline **15** (7.50 g, 35.0 mmol), allyl 2-aminobenzoate **22** and toluene (350 cm^3) yielding 12.15 g of crude product. Purfication was achieved on a silica gel column using a gradient elution 100% CH_2Cl_2 to 100% EtOAc yielding **16** (9.35 g, 71%) as a yellow oil (Found: C, 61.0; H, 6.0; N, 7.4. $C_{19}H_{22}N_2O_6$ requires C, 60.95; H, 5.9; N, 7.5%); ν_{max}(CH_2Cl_2)/cm^{-1} 3267, 3054, 2987, 2360, 2305, 1712, 1696, 1659, 1589, 1450, 1408, 1285 and 740; δ_H([^{2}H]$_6$DMSO, 70 °C) 2.08–2.25 (2 H, m, proline CH_2), 3.57 (2 H, m, NCH_2), 4.30–4.60 (4 H, m, C*H*OH, NCO_2CH_2 and OH), 4.80–4.95 (3 H, m, NCH and aryl CO_2CH_2), 5.05–5.44 (4 H, m, 2 × CH=CH_2), 5.85 (1 H, br m, carbamate C*H*=CH_2), 6.04 (1 H, m, aryl C*H*=CH_2), 7.17 (1 H, td, *J* 7.9 and 1.5, aryl), 7.59 (1 H, td, *J* 7.9 and 1.7, aryl), 7.98 (1 H, dd, *J* 7.9 and 1.5, aryl), 8.40 (1 H, dd, *J* 7.9, 1.7, aryl) and 10.87 (1 H, br s, NH); *m/z* (CI+) 375 (M + H)$^+$, 356, 335, 317, 291, 230, 198, 177, 170, 126, 108 and 86.

(2*S*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-4′-nitroprolinanilide 17. Method D was used in the preparation of **17** using EEDQ (11.20 g, 40.1 mmol), allyloxycarbonyl protected (2*S*,4*R*)-4-hydroxyproline **15** (7.50 g, 35.0 mmol), 4-nitroaniline (6.79 g, 49.2 mmol) and toluene (250 cm^3). Dry THF (20 cm^3) was added to aid solubility of the 4-nitroaniline. The reaction yielded **17** (6.33 g, 54%) as a pale yellow solid after purification using silica gel chromatography (100% EtOAc), mp 163–165 °C (Found: C, 53.7; H, 5.1; N, 12.4. $C_{15}H_{17}N_3O_6$ requires C, 53.7; H, 5.1; N, 12.5%); ν_{max}(Nujol mull)/cm^{-1} 3329, 1705, 1670, 1458, 1377, 1179, 1083 and 770; δ_H([^{2}H]$_6$DMSO, 70 °C) 1.97–2.30 (2 H, m, proline CH_2), 3.40–3.59 (2 H, m, NCH_2), 4.35 (1 H, br s, OH), 4.43 (3 H, m, C*H*OH and OCH_2), 4.86 (1 H, br s, NCH), 5.11–5.26 (2 H, m, CH=CH_2), 5.83 (1 H, m, C*H*=CH_2), 7.83 (2 H, m, aryl), 8.16 (2 H, m, aryl) and 10.35 (1 H, br s, NH); *m/z* (FAB+) 336 (M + H)$^+$, 316, 281, 259, 218, 170, 123, 108 and 105.

(2*S*,4*R*)-1-Allyloxycarbonyl-4-hydroxy-2′-nitroprolinanilide 18. Method D was used in the preparation of **18** using EEDQ (11.20 g, 40.1 mmol), allyloxycarbonyl protected (2*S*,4*R*)-4-hydroxyproline **15** (7.50 g, 35.0 mmol), 2-nitroaniline (6.79 g, 49.2 mmol) and toluene (250 cm^3). The reaction yielded **18** (5.51 g, 47%) as a dark yellow oil (Found: C, 53.7; H, 5.2; N, 12.4. $C_{15}H_{17}N_2O_2$ requires C, 53.7; H, 5.1; N, 12.5%); ν_{max}(Nujol mull)/cm^{-1} 3438, 3337, 3086, 2945, 1715, 1698, 1649, 1608, 1586, 1503, 1436, 1411, 1342, 1279, 1044, 991, 968, 932, 861, 771, 744 and 691; δ_H($CDCl_3$) 2.19–2.60 (2 H, m, proline CH_2), 3.52–3.90 (3 H, m, C*H*OH and NCH_2), 4.45–4.65 (3 H, m, NCH and OCH_2), 5.00–5.45 (2 H, m, CH=CH_2), 5.91 (1 H, m, C*H*=CH_2), 7.21 (1 H, m, aryl), 7.66 (1 H, m, aryl), 8.19 (1 H, m, aryl), 8.68 (1 H, m, aryl) and 10.83 (1 H, br s, NH); *m/z* (FAB+) 336 (M + H)$^+$, 316, 281, 259, 218, 170, 123, 108 and 105.

(2*S*,4*R*)-1-(*p*-Nitrobenzyloxycarbonyl)-4-hydroxyprolinanilide 4. Method D was used in the synthesis of **4** using (2*S*,4*R*)-1-(*p*-nitrobenzyloxycarbonyl)-4-hydroxyproline **13** (7.50 g, 24.2 mmol), aniline (2.00 g, 21.5 mmol) and EEDQ (9.00 g, 36.4 mmol) in toluene (120 cm^3). The reaction was stirred at room temperature for 18 h. The product was precipitated, filtered and washed with ether giving **4** (6.87 g, 83%) as white crystals, mp 181–182 °C (from EtOAc–hexane) (Found: C, 59.2; H, 4.7; N, 10.9. $C_{19}H_{19}N_3O_6$ requires C, 59.4; H, 4.7; N, 10.9%); *m/z* 386 (M + H)$^+$; δ_H([^{2}H]$_6$DMSO) 1.91–2.06 (1 H, m, proline CH_2), 2.11–2.28 (1 H, m, proline CH_2), 3.39–3.64 (2 H, m, NCH_2), 4.32 (1 H, br s, OH), 4.45 (1 H, m, C*H*OH), 5.15 (3 H, m, NCH and NCO_2CH_2), 7.02 (1 H, t, *J* 6.7, phenyl), 7.26 (2 H, m, phenyl), 7.57 (2 H, t, *J* 6.7, phenyl), 7.47 and 7.89, 7.62 and 8.23

(4 H, two pairs of *o*-coupling d of the *p*-nitrobenzyl ring, *J* 8.3, representing two rotamers) and 10.01 and 10.08 (1 H, two s, NHs of two rotamers).

Method E: 5-allyloxycarbonyl-2-(3-allyloxycarbonylphenyl)-2,5-diazabicyclo[2.2.1]heptan-3-one 2

Diethyl azodicarboxylate (DEAD) (4.04 g, 23.0 mmol) was added dropwise over 10 min to a solution of **1** (5.00 g, 13.4 mmol) and triphenylphosphine (13.39 g, 51.1 mmol) in dry THF (250 cm^3) with stirring under argon at −10 °C. After 1 h the reaction mixture was allowed to warm to room temperature and was stirred overnight. The mixture was then evaporated to dryness and purified by column chromatography using silica gel and 50% EtOAc–CH_2Cl_2 as eluent which yielded **2** (1.13 g, 28%) as a colourless oil plus some impure fractions (Found: C, 64.0; H, 5.7; N, 7.8. $C_{19}H_{20}N_2O_5$ requires C, 64.0; H, 5.7; N, 7.9%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3312, 2984, 1800, 1740, 1725, 1648, 1492, 1448, 1378, 1263, 1104 and 759; $\delta_H([^2H]_6DMSO)$ 2.00–2.10 (1 H, br d, J_{AB} 10.0, bridge CH), 2.15–2.25 (1 H, d, J_{AB} 10.0, bridge CH), 3.54 (2 H, m, NCH_2), 4.56 (3 H, br s, NC*H*C=O and NCO_2CH_2), 4.82 (2 H, m, aryl CO_2CH_2), 5.06 (1 H, s, O=CNC*H*), 5.15–5.45 (4 H, m, 2 × CH=CH_2), 5.88–6.11 (2 H, m, 2 × C*H*=CH_2), 7.55 (1 H, t, *J* 7.9, aryl), 7.76 (2 H, m, aryl) and 8.30 (1 H, m, aryl); *m/z* (GC–MS) 355 $(M - H)^+$, 249, 176, 130, 104, 75, 59 and 44.

5-Allyloxycarbonyl-2-(2-allyloxycarbonylpheny)-2,5-diazabicyclo[2.2.1]heptan-3-one 23. Method E was used in the preparation of **23** using DEAD (2.79 g, 16.0 mmol) and triphenylphosphine (5.25 g, 20.0 mmol) with **16** (5.00 g, 13.0 mmol). Purification was achieved by column chromatography (ether) yielding pure **23** (2.51 g, 53%) as a colourless oil (Found: C, 63.4; H, 5.8; N, 7.5. $C_{19}H_{20}N_2O_5$ requires C, 63.8; H, 5.8; N, 7.8%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3055, 2986, 2893, 1727, 1705, 1649, 1601, 1451, 1409, 1389, 1358, 1265 and 741; $\delta_H([^2H]_6DMSO$, 70 °C) 1.98–2.02 (1 H, d, J_{AB} 9.9, bridge CH), 2.21–2.25 (1 H, d, J_{AB} 9.9, bridge CH), 3.54 (2 H, m, NCH_2), 4.46 (1 H, d, *J* 0.7, NC*H*C=O), 4.56 (2 H, m, NCO_2CH_2), 4.67 (3 H, m, O=CNC*H* and aryl CO_2CH_2), 5.16–5.39 (4 H, m, 2 × CH=CH_2), 5.88–6.11 (2 H, m, 2 × C*H*=CH_2), 7.28–7.38 (2 H, m, aryl), 7.58 (1 H, td, *J* 7.7 and 1.5, aryl) and 7.76 (1 H, dd, *J* 7.8 and 1.3, aryl); *m/z* (FAB+) 357 $(M + H)^+$, 299, 271, 205, 178 and 108.

5-Allyloxycarbonyl-2-(4-nitrophenyl)-2,5-diazabicyclo[2.2.1]-heptan-3-one 24. Method E was used in the formation of **24** using DEAD (2.18 g, 13.0 mmol), triphenylphosphine (4.10 g, 16.0 mmol) and **17** (3.50 g, 10.0 mmol) in dry THF (150 cm^3) at −10 °C under argon. The mixture, after being allowed to warm to room temperature overnight, was evaporated to dryness to give a yellow impure solid. Recrystallisation yielded pure **24** (2.28 g, 69%) as a pale yellow solid, mp 177–179 °C (from EtOAc–hexane) (Found: C, 56.75; H, 4.8; N, 13.1. $C_{15}H_{15}N_3O_5$ requires C, 56.8; H, 4.8; N, 13.2%); ν_{max}(Nujol mull)/cm^{-1} 2947, 2868, 2845, 1720, 1692, 1646, 1594, 1510, 1498, 1461, 1375, 1320, 1186, 1114, 997, 923, 850 and 753; $\delta_H([^2H]_6DMSO)$ 2.05–2.15 (1 H, d, J_{AB} 10.0, bridge CH), 2.18–2.25 (1 H, d, J_{AB} 10.0, bridge CH), 3.34–3.70 (2 H, m, NCH_2), 4.50–4.65 (3 H, m, NC*H*C=O and NCO_2CH_2), 5.16–5.40 (3 H, m, O=CNC*H* and CH=CH_2), 5.82–5.96 (1 H, m, C*H*=CH_2), 7.87 (2 H, m, aryl) and 8.26 (2 H, m, aryl); *m/z* (FAB+) 318 $(M + H)^+$, 290, 279, 260, 243, 232, 226, 218, 206, 199, 186, 176, 166, 158, 149, 131, 123 and 108.

5-Allyloxycarbonyl-2-(2-nitrophenyl)-2,5-diazabicyclo[2.2.1]-heptan-3-one 25. Method E was used in the formation of **25** using DEAD (2.18 g, 13.0 mmol), triphenylphosphine (4.10 g, 16.0 mmol) and **18** (3.50 g, 10.0 mmol) in dry THF (150 cm^3) at −10 °C under argon. The mixture, after being allowed to warm to room temperature overnight, was evaporated to dryness to give a yellow oil. This was then purified using silica gel column chromatography (25% EtOAc–hexane) to give pure **25** (2.47 g, 78%) as a dark yellow solid (Found: C, 56.8; H, 4.9; N, 13.1. $C_{15}H_{15}N_3O_5$ requires C, 56.8; H, 4.8; N, 13.2%); ν_{max}(Nujol mull)/cm^{-1} 2923, 2853, 1722, 1699, 1650, 1601, 1536, 1464, 1393, 1356, 1281, 1172, 1137, 1112, 926, 786 and 650; $\delta_H([^2H]_6$-DMSO, 70 °C) 2.05–2.13 (1 H, d, J_{AB} 10.1, bridge CH), 2.20–2.30 (1 H, d, J_{AB} 10.1, bridge CH), 3.61 (2 H, s, NCH_2), 4.50 (1 H, s, NC*H*C=O), 4.58 (2 H, m, OCH_2), 4.87 (1 H, s, O=CNC*H*), 5.15–5.35 (2 H, m, CH=CH_2), 5.85–5.98 (1 H, m, C*H*=CH_2), 7.47 (1 H, td, *J* 7.9 and 1.1, aryl), 7.55 (1 H, dd, *J* 7.9 and 1.1, aryl), 7.75 (1 H, td, *J* 7.9 and 1.4, aryl) and 7.94 (1 H, dd, *J* 7.9 and 1.4, aryl); *m/z* (FAB+) 318 $(M + H)^+$, 296, 290, 279, 260, 244, 232, 231, 225, 218, 206, 199, 192, 186, 175, 165, 159, 149, 131, 123 and 108.

2-Phenyl-5-(*p*-nitrobenzyloxycarbonyl)-2,5-diazabicyclo-[2.2.1]heptan-3-one 5. Method E was used to make **5** using the anilide **4** (1.00 g, 2.60 mmol) and triphenylphosphine (1.00 g, 3.81 mmol) in THF (25 cm^3). DEAD (0.55 g, 3.18 mmol) was added and the reaction was stirred under argon at −10 °C overnight. The solvents were evaporated and the residue was purified by flash chromatography on silica eluting with CH_2Cl_2, then CH_2Cl_2–EtOAc giving **5** as a white solid (0.48 g, 50%), mp 147–148 °C (Found: C, 61.8; H, 4.6; N, 11.5. $C_{19}H_{17}N_3O_5$ requires C, 62.1; H, 4.6; N, 11.4); *m/z* 368 $(M + H)^+$; $\delta_H(CDCl_3 + [^2H]_6DMSO)$ 2.05 (1 H, br d, J_{AB} 10.1, bridge CH), 2.25 (1 H, br d, J_{AB} 10.1, bridge CH), 3.56–3.71 (2 H, two dd, *J* 11.5 and 1.4, NCH_2), 4.70 (1 H, br s, NC*H*C=O), 4.74 (1 H, br s, O=CNC*H*), 5.20 (1 H, d, J_{AB} 13.3, OCH_2), 5.32 (1 H, d, J_{AB} 13.3, OCH_2), 7.15 (1 H, t, *J* 7.2, phenyl), 7.27–7.49 (4 H, m, phenyl) and 7.56 and 8.21 (4 H, two d, *J* 8.7, *p*-nitrobenzyl ring).

Method F: 2-(3-carboxyphenyl)-2,5-diazabicyclo[2.2.1]heptan-3-one 3

Tetrakis(triphenylphosphine)palladium(0) (0.36 g, 0.33 mmol) was added to a solution of **2** (3.59 g, 10.0 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (3.63 g, 25.0 mmol) in dry CH_2Cl_2 (100 cm^3) with stirring at room temperature under argon. Almost immediately a white precipitate was seen and the reaction was left for a further 2 h to go to completion. This was assumed when evolution of all gases had ceased. The reaction mixture was filtered, washing well with CH_2Cl_2, and allowed to dry yielding **3** (1.65 g, 70%) as a fine white powder, mp 137 °C (decomp.) (Found: C, 61.9; H, 5.3; N, 12.1. $C_{12}H_{12}N_2O_3$ requires C, 62.1; H, 5.2; N, 12.1%); ν_{max}(Nujol mull)/cm^{-1} 3392, 3051, 2924, 2854, 2725, 2685, 2520, 2362, 1720, 1716, 1628, 1558, 1448, 1377, 1204, 1178 and 745; $\delta_H([^2H]_6DMSO)$ 1.70–1.80 (1 H, d, J_{AB} 9.9, bridge CH), 1.95–2.05 (1 H, d, J_{AB} 9.9, bridge CH), 2.85 (1 H, d, J_{AB} 9.7 HNCH_2), 2.98 (1 H, d, J_{AB} 9.7, HNCH_2), 3.71 (1 H, s, HNC*H*C=O), 4.87 (1 H, s, O=CNC*H*), 5.10 (1 H, br s, NH), 7.48 (1 H, t, *J* 7.9, aryl), 7.72 (2 H, m, aryl) and 8.20 (1 H, m, aryl); *m/z* (FAB+) 233 $(M + H)^+$, 204, 188, 149, 121 and 105.

2-(2-Carboxyphenyl)-2,5-diazabicyclo[2.2.1]heptan-3-one 26. Method F was used in the synthesis of **26**. Tetrakis(triphenylphosphine)palladium(0) (0.743 g, 0.643 mmol), **23** (2.29 g, 6.43 mmol), Meldrum's acid (2.31 g, 16.0 mmol) and dry CH_2Cl_2 (30 cm^3) were used, yielding 1.15 g of a yellow powder after filtration. The powder was dissolved in water and extracted using CH_2Cl_2. The yellow aqueous layer was totally decolorised at room temperature using carbon (0.25 g), filtered and evaporated under high vacuum (0.1 mmHg) to yield **26** (1.05 g, 70%) as a white powder, mp 237–238 °C (Found: C, 62.1; H, 5.2; N, 12.0. $C_{12}H_{12}N_2O_3$ requires C, 62.1; H, 5.2; N, 12.1%); ν_{max}(Nujol mull)/cm^{-1} 3390, 3040, 2852, 2725, 2359, 1722, 1718, 1579, 1541, 1456, 1377, 1147, 1058 and 732; $\delta_H(D_2O)$ 2.15–2.25 (1 H, d, J_{AB} 11.4, bridge CH), 2.65–2.75 (1 H, d, J_{AB} 11.4, bridge CH), 3.62 (1 H, d, J_{AB} 11.4, HNCH_2), 3.71 (1 H, d, J_{AB} 11.4, HNCH_2), 4.55 (1 H, s, HNC*H*C=O), 4.82 (1 H, s, O=CNC*H*), 7.30 (1 H, dd, *J* 7.6 and 1.8, aryl), 7.42–7.55 (2 H, m, aryl) and 7.63 (1 H, dd, *J* 7.6 and 1.8, aryl); *m/z* (FAB+) 233 $(M + H)^+$, 226, 215, 205, 186, 165, 150, 128, 123, 115 and 105.

2-(4-Nitrophenyl)-2,5-diazabicyclo[2.2.1]heptan-3-one 27. Method F was used in the synthesis of **27**. Tetrakis(triphenyl-

phosphine)palladium(0) (0.100 g, 0.087 mmol), **24** (0.275 g, 0.867 mmol), Meldrum's acid (1.60 g, 11.11 mmol) and dry CH_2Cl_2 (20 cm^3) were reacted under argon until all release of gases had ceased (1 h). The reaction mixture was taken to pH 2 using 2 M hydrochloric acid and the aqueous layer extracted with CH_2Cl_2 before being taken to pH 12 with saturated aqueous sodium hydrogen carbonate. This was then re-extracted using EtOAc, the combined organics were dried with Na_2SO_4, filtered and evaporated to give pure **27** (0.121 g, 60%) as a pale yellow solid, mp 173–175 °C (Found: C, 56.5; H, 4.8; N, 17.8. $C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.75; N, 18.0%); ν_{max}(Nujol mull)/cm^{-1} 3335, 2923, 2856, 1709, 1594, 1507, 1461, 1374, 1342, 1295, 1196, 1113, 1033, 976, 852, 821, 779 and 719; δ_H($CDCl_3$) 1.69 (1 H, br s, NH), 1.91–1.98 (1 H, d, J_{AB} 10.0, bridge CH), 2.04–2.12 (1 H, d, J_{AB} 10.0, bridge CH), 3.03 (1 H, d, J_{AB} 9.9, HNCH_2), 3.29 (1 H, d, J_{AB} 9.9, HNCH_2), 3.88 (1 H, d, *J* 0.8, HNC*H*C=O), 4.75 (1 H, s, O=CNC*H*), 7.69 (2 H, m, aryl) and 8.24 (2 H, m, aryl); *m/z* (GC–MS) 234 $(M + H)^+$, 205, 177, 149, 129, 103, 90, 76, 68, 56 and 41.

2-(2-Nitrophenyl)-2,5-diazabicyclo[2.2.1]heptan-3-one 28. Method F was used in the synthesis of **28**. Tetrakis(triphenylphosphine)palladium(0) (0.364 g, 0.32 mmol), **25** (1.00 g, 3.2 mmol), Meldrum's acid (0.568 g, 3.9 mmol) and dry CH_2Cl_2 (30 cm^3) were used. No solid could be seen out of solution. The organics were evaporated to dryness and the residue taken up into 2 M hydrochloric acid and this was washed with CH_2Cl_2 before being taken to pH 10 using solid sodium hydrogen carbonate. The aqueous layer was re-extracted with CH_2Cl_2 and the combined organics dried using Na_2SO_4, filtered and evaporated to dryness to give impure amine **28** (0.45 g) as a yellow foam. Purification of the product by silica gel chromatography (EtOAc) yielded pure **28** (0.387 g, 53%) as a yellow oil (Found: C, 56.6; H, 4.6; N, 17.9. $C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.75, N, 18.0%); ν_{max}(CH_2Cl_2)/cm^{-1} 3054, 2984, 2361, 1716, 1604, 1533, 1487, 1388, 1266 and 740; δ_H($CDCl_3$) 1.86–1.95 (1 H, d, J_{AB} 9.9, bridge CH), 2.15–2.25 (1 H, d, J_{AB} 9.9, bridge CH), 2.35 (1 H, br s, NH), 3.17 (1 H, d, J_{AB} 9.9, HNCH_2), 3.25 (1 H, d, J_{AB} 9.9, HNCH_2), 3.83 (1 H, t, *J* 0.9, HNC*H*C=O), 4.58 (1 H, d, *J* 0.6, O=CNC*H*), 7.28–7.41 (2 H, m, aryl), 7.63 (1 H, td, *J* 7.7 and 1.7, aryl) and 7.91 (1 H, dd, *J* 8.1 and 1.7, aryl); δ_H($CDCl_3$–D_2O shake) Loss of NH signal at δ 2.35; *m/z* (FAB+) 234 $(M + H)^+$, 228, 218, 206, 192, 167, 149, 131 and 123.

2-Phenyl-2,5-diazabicyclo[2.2.1]heptan-3-one 6

A solution of **5** (2.6 g) in dry THF (100 cm^3) containing 10% palladium on charcoal (400 mg) was hydrogenated for 2.5 h. The catalyst was removed by filtration and the solvents evaporated to dryness. The yellow oil was purified by flash chromatography eluting with EtOAc, then 10% methanol–EtOAc to give **6** (1.2 g, 88%) as a white solid, mp 83–84 °C (from hexane); *m/z* 189 $(M + H)^+$; δ_H($CDCl_3$) 1.83 (1 H, d, J_{AB} 9.9, bridge CH), 1.87 (1 H, br s, NH), 2.03 (1 H, d, J_{AB} 9.9, bridge CH), 3.03 (1 H, dd, *J* 9.7 and 1.6, NCH_2), 3.21 (1 H, dd, *J* 9.7 and 1.6, NCH_2), 3.83 (1 H, br s, O=CNC*H*), 4.62 (1 H, br s, NC*H*C=O), 7.19 (1 H, t, *J* 7.4, phenyl), 7.36 (2 H, t, *J* 7.4, phenyl) and 7.49 (2 H, d, *J* 7.4, phenyl).

(2*S*,4*R*)-*N*-Benzyl-4-hydroxy-1-(*p*-nitrobenzyloxycarbonyl)-prolinamide 7

A solution of (2*S*,4*R*)-1-(*p*-nitrobenzyloxycarbonyl)-4-hydroxyproline **13** (3.00 g, 9.68 mmol) in dry THF (100 cm^3) was cooled at −10 °C. To the stirred solution triethylamine (1.23 g, 12.20 mmol) was added followed by isobutyl chloroformate (1.68 g, 12.34 mmol). After 15 min benzylamine (1.08 g, 10.10 mmol) was added and the mixture was allowed to come to room temperature overnight. A white precipitate was filtered and the filtrate was evaporated to dryness yielding a white solid residue. Both solids were shown to be mainly the required product **7** (2.25 g, 58%), mp 180–182 °C (from EtOAc) (Found: C, 59.9; H, 5.4; N, 10.4. $C_{20}H_{21}N_3O_6$ requires C, 60.1; H, 5.3; N, 10.4%); *m/z* 400 $(M + H)^+$; δ_H([^{2}H]$_6$DMSO) 1.83–1.98 (1 H, m, proline CH_2), 2.04–2.23 (1 H, m, proline CH_2), 3.30 (1 H, br s, OH), 3.40–3.60 (2 H, m, NCH_2), 4.21–4.43 (4 H, m, NCH_2Ar, C*H*OH and NC*H*=O), 5.15 and 5.22 (2 H, two s, rotamers, OCH_2), 7.15–7.35 (5 H, m, phenyl), 7.52 and 8.11, 7.63 and 8.18 (4 H, two pairs of d, *J* 8.4, representing *ortho* couplings of two rotamers) and 8.47 and 8.58 (1 H, two t, *J* 6.3, NH of rotamers).

Attempted cyclisation of 7 and isolation of 8

When **7** (0.50 g, 1.25 mmol) was subjected to similar Mitsunobu cyclisation conditions as for **1**, no bicyclic structures were isolated. After a similar work-up and flash chromatography (twice, to remove triphenylphosphine oxide) eluting with an EtOAc–hexane gradient, (2*S*,4*S*)-*N*-benzyl-4-[1,2-bis(ethoxycarbonyl)hydrazino]-1-(*p*-nitrobenzyloxycarbonyl)prolinamide **8** was isolated (0.30 g, 43%), mp 187–189 °C (from EtOAc–hexane) (Found: C, 56.0; H, 5.7; N, 12.3. $C_{26}H_{31}N_5O_9$ requires C, 56.0; H, 5.7; N, 12.6%); *m/z* 558 $(M + H)^+$; δ_H($CDCl_3$) 1.19–1.30 (6 H, m, 2 × CH_2CH_3), 2.28–2.62 (2 H, 2 br m, CH_2), 3.51–3.62 (1 H, m, NCH_2), 3.79–3.92 (1 H, m, NCH_2), 4.12–4.24 (4 H, 2 q, *J* 6.3, 2 × CH_2CH_3), 4.28–4.37 (1 H, m, NCH), 4.43 (2 H, br s, NHCH_2Ar), 4.70–4.88 (1 H, m, NC*H*C=O), 5.18 (2 H, br s, OCH_2), 6.80–7.05 (2 H, br s, NH), 7.19–7.31 (5 H, m, phenyl) and 7.44 and 8.14 (4 H, *ortho* coupling d, *J* 8.3, *p*-nitrobenzyl).

Method G: 2-(3-carboxyphenyl)-5-phenylacetyl-2,5-diazabicyclo[2.2.1]heptan-3-one 9

Phenylacetyl chloride (0.167 g, 1.1 mmol) was slowly added to a solution of **3** (0.250 g, 1.1 mmol) and triethylamine (0.109 g, 1.1 mmol) in DMF (25 cm^3) at 0 °C with stirring. The reaction was left for 4 h before being evaporated to dryness, taken up into EtOAc and washed with 2 M hydrochloric acid. The organics were dried using anhydrous sodium sulfate, filtered and evaporated to give 0.2 g of impure solid. The product was purified using silica gel column chromatography (1% acetic acid–EtOAc) to give **9** (0.104 g, 28%) as a white powder, mp 162–164 °C [Found: C, 64.4; H, 5.4; N, 6.9. $C_{20}H_{18}N_2O_4 \cdot C_2H_4O_2$ (acetic acid) requires C, 64.4; H, 5.4; N, 6.8%]; ν_{max}(Nujol mull)/cm^{-1} 2932, 1727, 1700, 1650, 1579, 1461, 1376, 1287, 1062 and 719; δ_H(CD_3OD, 50 °C) 2.07–2.26 (2 H, m, bridge CH_2), 3.65 (2 H, s, PhCH_2), 3.53–3.87 (2 H, m, NCH_2), 4.77–4.99 (2 H, m, NC*H*C=O and O=CNC*H*), 7.23 (5 H, m, *Ph*CH$_2$), 7.43 (1 H, m, aryl), 7.64–7.79 (2 H, m, aryl) and 8.10 (1 H, m, aryl); *m/z* (FAB+) 351 $(M + H)^+$, 333, 322, 204, 165 and 118.

2(2-Carboxyphenyl)-5-phenylacetyl-2,5-diazabicyclo[2.2.1]-heptan-3-one 10. Method G was used in the preparation of **10**. Water (2 cm^3) was added as a co-solvent to aid solubility. Amino acid **26** (0.50 g, 2.2 mmol), phenylacetyl chloride (1.00 g, 6.6 mmol), triethylamine (0.654 g, 6.6 mmol) and DMF (25 cm^3)–water (2 cm^3) yielded **10** (0.695 g, 92%) as a yellow foam after purification by silica gel column chromatography (1% acetic acid–EtOAc) and high vacuum (0.1 mmHg) (Found: C, 68.5; H, 5.2; N, 7.9. $C_{20}H_{18}N_2O_4$ requires C, 68.6; H, 5.2; N, 8.0%); ν_{max}(CH_2Cl_2)/cm^{-1} 3054, 2986, 2614, 1724, 1719, 1672, 1654, 1600, 1493, 1457, 1390, 1286 and 738; δ_H([^{2}H]$_6$DMSO) 2.04–2.31 (2 H, m, bridge CH_2), 3.44–3.71 (4 H, m, NCH_2 and PhCH_2), 4.64 (1 H, s, NC*H*C=O), 4.76 (1 H, s, O=CNC*H*), 7.18–7.39 (7 H, m, aryl and *Ph*CH$_2$), 7.57 (1 H, m, aryl) and 7.71 (1 H, m, aryl); *m/z* (FAB+) 351 $(M + H)^+$, 205 and 186.

2-(4-Nitrophenyl)-5-phenylacetyl-2,5-diazabicyclo[2.2.1]-heptan-3-one 11. Method G was used in the preparation of **11**. Amine **27** (0.250 g, 1.07 mmol) was dissolved in CH_2Cl_2 (25 cm^3) at 0 °C with stirring under nitrogen. To this was added triethylamine (0.130 g, 1.29 mmol) followed by the dropwise addition of phenylacetyl chloride (0.200 g, 1.29 mmol). The reaction mixture was stirred for 2 h before being washed with 2 M hydrochloric acid, water and then saturated aqueous sodium hydrogen carbonate. The organics were dried with

Na_2SO_4, filtered and evaporated to leave 0.49 g of an impure yellow solid. This was triturated using hot CH_2Cl_2 to yield after decantation pure **11** (0.320 g, 85%) as a yellow solid, mp 236–238 °C (Found: C, 65.0; H, 5.0; N, 11.8. $C_{19}H_{17}N_3O_4$ requires C, 64.95; H, 4.9; N, 12.0%); ν_{max}(Nujol mull)/cm^{-1} 2954, 2922, 2853, 1719, 1662, 1599, 1509, 1463, 1399, 1376, 1349, 1308, 1204, 1118, 982, 847 and 718; δ_H([^{2}H]$_6$DMSO, 70 °C) 1.97–2.35 (2 H, m, bridge CH_2), 3.63 (2 H, s, PhCH_2), 3.55–3.90 (2 H, m, NCH_2), 4.90 (1 H, s, NC*H*C=O), 5.16 (1 H, s, O=CNC*H*), 7.21 (5 H, m, *Ph*CH_2), 7.85 (2 H, d, *J* 9.2, aryl) and 8.24 (2 H, d, *J* 9.2, aryl); *m/z* (FAB+) 352 (M + H)$^+$, 336, 165, 150, 123 and 115.

2-(2-Nitrophenyl)-5-phenylacetyl-2,5-diazabicyclo[2.2.1]-heptan-3-one 12. Method G was used in the synthesis of **12**. Amine **28** (0.200 g, 0.86 mmol), triethylamine (0.104 g, 1.03 mmol), phenylacetyl chloride (0.159 g, 1.03 mmol) and CH_2Cl_2 (25 cm^3) were reacted to give after work-up impure **12** (0.56 g) as a yellow oil. This was purified by silica gel chromatography (EtOAc) to yield pure **12** (0.30 g, 99%) as a yellow foam, mp 55–57 °C (Found: C, 64.7; H, 4.9; N, 11.8. $C_{19}H_{17}N_3O_4$ requires C, 64.95; H, 4.9; N, 12.0%); ν_{max}(CH_2Cl_2)/cm^{-1} 3056, 2985, 2888, 1727, 1654, 1604, 1582, 1533, 1488, 1453, 1389, 1354, 1303, 1286, 1206, 1167, 1004, 937, 853, 736 and 703; δ_H([^{2}H]$_6$DMSO) 1.96–2.30 (2 H, m, bridge CH_2), 3.53–3.80 (4 H, m, NCH_2 and PhCH_2), 4.82 (1 H, s, NC*H*C=O), 4.86 (1 H, s, O=CNC*H*), 7.20–7.31 (5 H, m, *Ph*CH_2), 7.41 (2 H, m, aryl), 7.73 (1 H, t, *J* 7.8, aryl) and 7.95 (1 H, dd, *J* 7.8 and 1.5, aryl); *m/z* (FAB+) 352 (M + H)$^+$, 206 and 108.

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